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A STUDY OF NON-GONOCOCCAL URETHRITIS, PRESUMABLY VENEREAL IN ORIGIN, BASED UPON 588 INFECTIONS IN 529 PATIENTS*

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This study of non-gonococcal urethritis had three objectives :

(1) To obtain an adequate clinical picture of non-gonococcal urethritis ;
(2) to determine the aetiology ;
(3) to outline a method of treatment.

The following definitions were used in this study :

Non-Gonococcal Urethritis.—All inflammatory processes of the male urethra presumed due to sexual intercourse, which were not caused by *N. gonorrhoea, H. ducreyi, T. pallidum*, the tubercle bacillus, protozoan, metazoan organisms, fungi, mechanical irritants, or tumours, were classified as non-gonococcal urethritis.

Acute Urethritis, Non-Gonococcal.—Non-gonococcal urethral infections in which the onset of the disease had occurred less than one month before the first visit to the clinic.

Chronic Urethritis, Non-Gonococcal.—Non-gonococcal urethral infections in which the onset of the disease had occurred more than one month before the first visit to the clinic.

Posterior Non-Gonococcal Urethritis.—A diagnosis of posterior urethritis was made when the gross pyuria was seen in two or more glasses of the multi-glass urine test.

Concurrent Gonorrhoea.—This term was limited to that gonorrhoeal infection immediately preceding the onset of the non-gonococcal urethritis.

Cure.—No patient was considered cured who had not been free of demonstrable discharge and gross pyuria for a minimum of 2 weeks, and who suffered no relapse after heavy drinking, prostatic massage, urethral dilatation, cystoscopy, heavy work, sports, or masturbation.

Failure.—Patients whose urethritis did not respond to one or more courses of antibiotic therapy, and controls whose disease did not subside spontaneously in 8 weeks, were considered failures.

Relapse.—A patient was considered to have had a relapse when his discharge or gross pyuria recurred following a clinical remission, but before the criteria for "cure" had been met, in the absence of coitus, and obvious evidence of re-infection.

Re-Infection.—A patient was considered to have a re-infection when his discharge recurred after the criteria for "cure" had been met and a history of coitus elicited, or when an unequivocally new organism could be demonstrated in his discharge, such as the appearance of previously non-existent *N. gonorrhoea.*

MATERIAL AND METHODS

The patients studied were Korean evacuees and personnel from Army and Air Force installations within a 100-mile radius of the 141st General Hospital. Referring organizations submitted complete histories, including pertinent data regarding dates of exposure, state of sobriety, and previous treatment.

In obtaining specimens for culture the urethra was gently milked, the prepuce retracted, the meatal lips separated, and a finely pointed sterile cotton applicator inserted into the globule of pus, care being taken to avoid scraping the urethral walls. Three swabs were thus obtained : one was examined fresh for protozoa and fungi, the other two were smeared on slides and planted in aerobic and anaerobic media respectively. Lankford's chocolate agar (Lankford, 1950) was used to isolate the Neisseria species, eosin methylene blue agar (Difco) to isolate the Gram-negative organisms of the enteric group, and 5 per cent. human blood agar plates for the aerobic organisms principally the Gram-positive pyogenic group. Sensitivity studies were executed using the paper disk method of Bondi, Spaulding, Smith, and Dietz (1947).

Patients were instructed to report to the clinic with full bladders, and a standard multi-glass urine test was performed at each visit. All patients were advised to abstain from alcohol, sexual excitement, coitus, heavy work, sports, and vigorous stripping of the urethra. Half of the patients were denied coffee, tea, carbonated beverages, and condiments. All patients were confined to barracks for the period of observation.

For 8 weeks 113 patients were used as controls and observed without treatment.

Penicillin was prescribed in doses ranging from 300,000 units twice daily to 600,000 units twice daily for 1 week ; streptomycin 0·5 g. twice daily for 1 week to 0·5 g. twice daily for 2 weeks ; chloramphenicol, aureomycin, and terramycin were given in weekly

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courses of 250 mg. every fourth hour on a 24-hr basis, up to a total of 3 weeks. All patients receiving chloramphenicol had a complete blood count before therapy, and this was repeated weekly during therapy.

Patients were seen at least once weekly until discharged. They were then observed in the follow-up clinic at monthly intervals for as long as 1 year.

RESULTS

Clinical Observations

Between January 1, 1951, and June 30, 1953, 2,486 cases of urethritis were seen; 1,943 proved to be cases of non-gonococcal urethritis, and 543 of gonorrhoea, a ratio of 3·6 to 1. Of the non-gonococcal infections, collected in 1952, 588 were intensively studied. They occurred in 529 individuals, only nine of whom were not Americans. Six of the patients were of Asiatic extraction, 78 were Negroes, and 445 Caucasians. The youngest was aged 17 years, the oldest 47; 75 per cent. were between the ages of 18 and 30 years. Only four patients denied exposure, but one of these had a concurrent gonorrhoea. A history of concurrent gonorrhoea was given by 101 patients (17·2 per cent.), a ratio of 5·8 to 1; 82 patients had had gonorrhoea previously and seventeen non-gonococcal urethritis; 329 had had neither concurrent gonorrhoea nor previous urethritis.

The incubation period could be accurately measured in only 435 of the infections studied; 79 had had concurrent gonorrhoea and 356 had not. The ranges of the incubation periods for gonorrhoea and non-gonococcal urethritis were identical, but a significantly larger percentage of the concurrent gonorrhoeal infections had an incubation period of 3 weeks or less.

Out of 101 patients with concurrent gonorrhoea 76 had no asymptomatic intervals between the completion of treatment for concurrent gonorrhoea and the onset of non-gonococcal urethritis. The majority stated, however, that the discharge did change its character following treatment for gonorrhoea and became less purulent and more scanty.

Altogether 47 patients, with supposedly uncomplicated gonorrhoea, were observed after receiving 300,000 units penicillin daily for 3 days: 23 of these patients (49 per cent.) subsequently developed a non-gonococcal urethritis, seventeen had no asymptomatic intervals, six had asymptomatic intervals ranging from 1 to 6 weeks. These six, however, had a gross pyuria throughout the asymptomatic period. The 24 patients, who did not develop non-gonococcal urethritis, had no gross pyuria following treatment of gonorrhoea.

Symptoms and Signs (Table I).—The presence of a concurrent gonorrhoea did not materially influence the character of the symptoms and signs seen in the 588 infections studied. In 68 patients with concurrent gonorrhoea the initial discharge decreased in character after treatment of the gonorrhoea with penicillin; in 33 there was no change. Of the 68 in whom the discharge decreased in quantity 25 had an asymptomatic interval ranging up to 6 weeks.

A discharge was complained of by 572 (97·2 per cent.) patients, but it could only be found in 555 (94·4 per cent.). Initially, it was profuse and purulent, resembling that of gonorrhoea, but quickly subsided into a thin, scant, watery droplet, seen chiefly in the morning.

Almost 50 per cent. of the patients complained of dysuria. In 25 per cent. it was mild and present chiefly when the patient first voided in the morning. In 24·5 per cent. it was rather severe and present throughout the day. It was usually worse at the onset of the disease, becoming less or disappearing when the discharge lost its gross purulent character. Dysuria, however, proved to be a misleading symptom, since it was often present in recently exposed individuals who had no other evidence of the disease, and was frequently absent in severe posterior urethritis.

Gross pyuria was observed in every patient. This varied at the onset from a clear first glass filled with fine, spiral shreds, to a grossly cloudy first glass containing uncountable large, fluffy,

TABLE I

SYMPTOMS AND SIGNS IN 588 NON-GONOCOCCAL URETHRAL INFECTIONS

Symptoms	No. of Cases	Per cent.
Discharge	572	97·2
Dysuria	291	49·5
Mild	147	25·0
Severe	144	24·5
Urethral itching	21	—
Haematuria	17	—
Frequency	15	—
Painful erections	12	—
Perineal soreness	11	—
Urgency	8	—
Suprapubic pain	7	—
Nocturia	6	—
Pain in scrotum	5	—
Backache	5	—
Pain in groin	3	—
Difficulty in voiding	2	—
Signs		
Gross pyuria	588	100·0
Discharge, total	555	94·4
Profuse and purulent	77	13·1
Profuse and watery or muco-purulent	108	18·4
Purulent droplet discharge	139	23·6
Watery droplet discharge	231	39·3
Haematuria, total	17	—
Gross admixed	2	—
Profuse terminal	4	—
Droplet terminal	11	—

TABLE II

ENDOSCOPIC FINDINGS IN 51 CASES OF NON-GONOCOCCAL URETHRITIS

Clinical Diagnosis	No. of Cases	Pendulous Urethra Only	To Urogenital Diaphragm	Intramembranous Urethra	Prostatic Urethra	Bladder
Acute anterior urethritis	14	(12) Desquam. exudate Superficial involvement of mucosa	(2) Same	0	0	0
Chronic anterior urethritis	12	(12) Same as above, but with occasional granulations	(12) Same	0	0	0
Acute posterior urethritis	13	(6) Severe mucosal reaction when involved	(6) Same	(13) Very intense reaction with hyperaemia, ulceration and bleeding	(13) Marked congestion and bleeding	(4) Intense haemorrhagic cystitis
Chronic posterior urethritis	12	(12) Milder reaction, more granulations than above	(12) Same	(12) Same with friable, bleeding mucosa	(12) Milder congestion but bleeds	0

purulent floccules. The intensity of the gross pyuria almost always varied with the severity of the discharge. Even in the most intense posterior urethritis, however, the second glass was never as cloudy as the first, and the gross pyuria was rarely observed in the other glasses. Close observation of the fluctuations of the gross pyuria at subsequent visits proved to be the most reliable means of evaluating the patient's progress.

The other symptoms and signs were neither statistically nor clinically significant.

Endoscopic Findings (Table II).—During the active phases of the disease 51 patients were cystourethroscoped. The clinical impression, based solely on the multi-glass urine test, was confirmed in all instances. An adequate and graphic description of the endoscopic findings is given by Harkness (1950a). Cystoscopy was very poorly tolerated.

After being cured of their disease 139 patients were cystoscoped. Those who responded promptly had no evidence of urethritis, but protracted cases occasionally demonstrated fine mucosal scars in the pendulous urethra.

Bacteriological Findings.—Altogether 1,390 cultures were taken from 574 patients ; 1,794 organisms were isolated in 1,229 cultures, while 161 cultures were sterile (11·5 per cent.). *Micrococcus pyogenes* was by far the most common organism isolated. There was no correlation between the organisms isolated and the clinical character of the disease.

Sensitivity Studies (Table III).—Chloramphenicol exhibited the widest *in vitro* sensitivity range, aureomycin the narrowest.

Complications.—28 patients were admitted with a posterior urethritis and concomitant prostatitis, sixteen more developed it during the course of treatment. Once the disease was presumptively cured, there was no evidence of prostatitis ; this was observed in 41 of the 44 patients with a posterior urethritis, the other three failed to return for a final evaluation.

No other complications were observed.

Sequelae.—One patient developed a stricture 8 months after initial infection. No other sequelae were seen.

TABLE III

IN VITRO SENSITIVITY TO FIVE ANTIBIOTICS OF THE 1,794 ISOLATES FROM 1,390 CULTURES IN 574 CASES OF NON-GONOCOCCAL VENEREAL URETHRITIS

Organism	Number of Patients with Organisms Sensitive to :				
	Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Terramycin
Micrococcus pyogenes	762	964	1,097	700	794
Beta Streptococcus	81	69	115	81	97
Gamma Streptococcus	71	83	100	82	85
Diphtheroids ..	73	86	92	62	76
Coliform Bacilli..	3	18	20	7	12
AlphaStreptococcus	17	8	23	22	25
Gaffky and Sarcina	15	15	15	12	12
Haemophilus ..	13	13	18	14	14
Non-pathogenic Neisseria ..	10	11	12	11	14
Aerobic Spore-forming Bacteria	5	10	9	8	10
Proteus and Pseudomonas..	4	9	6	4	8
Total	1,054	1,286	1,507	1,003	1,147
Percentage ..	58·8	71·7	84·0	55·9	63·9

Diagnostic Criteria.—The following diagnostic criteria for non-gonococcal venereal urethritis can be established :

(1) *Presence of a gross pyuria* ;
(2) Presence or recent history of urethral discharge ;

(3) Absence of any of the pathogens (enumerated in the original definition of the disease) in the urethral discharge ;

(4) History of previous sexual exposure.

Diagnostic Error.—The two most common sources of diagnostic error were failure to look for a gross pyuria and giving too much importance to smears. It was observed that if the discharge resembled that of gonorrhoea, and organisms morphologically like *N. gonorrhoea* were found abundantly in the smear, then a presumptive diagnosis of gonorrhoea was feasible. On the other hand, a scanty atypical discharge containing a few Gram-negative cocci should not be labelled gonorrhoea too hastily. If there were reasonable doubts a culture was indicated.

Exciting Factors.—The roles of intoxication, unusual forms of coitus, the menstrual status of partners, and the use of contraceptive jellies by contacts could not be evaluated, because the data were either scanty or too untrustworthy.

Prophylaxis.—The efficacy of the common prophylactic measures was too difficult to determine because no estimate of the incidence of the disease per modality could be made. However, 524 patients gave accurate information of the prophylaxis they used, or did not use, 302 patients used nothing, 91 condoms, 99 " pro kits ", and 32 both condoms and " pro kits ". Clinically, the disease seen following the use of a " pro kit " was indistinguishable from the others, the organisms isolated were identical in distribution, but there was a difference in the incidence of concurrent gonorrhoea. Those who used no prophylaxis had a 19·5 per cent. incidence of concurrent gonorrhoea ; those who wore condoms a 4 per cent. incidence ; those who used " pro kits " a 22·2 per cent. incidence ; and those who used both a 9·4 per cent. incidence.

Therapy

Of the 588 cases of non-gonococcal venereal urethritis studied, the effectiveness of therapy was fully evaluated in 440. Almost all of those considered to be well were followed for an additional month after being declared cured, half for 3 to 6 months, and a quarter from 6 months to a year. Nine of the patients were under treatment from 4 to 7 months. One patient, treated for 7 months was still infected 6 months after completing therapy and was considered a therapeutic failure. The other 439 patients, both those treated and the controls, were discharged as cured.

Altogether 113 controls were initially observed for 8 weeks without treatment, seven of whom failed to cooperate. In 62 of the remaining 106 (58·5 per cent.), the disease subsided spontaneously in a characteristic manner : there was a gradual disappearance of all signs and symptoms, and no relapses. Of the 44 failures eighteen had induced relapses which followed apparent remissions. Eleven patients with acute urethritis in the control group had previously been given penicillin for their concurrent gonorrhoea. Ten of these were well in 8 weeks. Nine of the control patients had abacterial infections, and only two of these were well at the end of the period of observation, serial cultures having been done weekly for as long as 4 weeks.

Specific Therapy.—464 patients, including the 44 patients in the control group in whom the disease failed to subside spontaneously, were treated with one or more courses of an antibiotic. Of these, 377 were cured, one was not, and 86 failed to meet the criteria for cure and could not be evaluated. 251 patients (66·4 per cent.) were cured by the first course of medication : 43 of these had abacterial infections (97·7 per cent. of 44), and the remaining 208 (62·3 per cent.) bacterial infections. These 251 cases were observed over an average of 4 weeks and 3 days. The 126 bacterial infections not cured by one course required 3·4 courses of medication, and were under continuous observation for an average of 10 weeks and 5 days before a final assessment was made.

The response, when antibiotics were effective, was an abrupt cessation of all signs and symptoms without relapse. The 126 patients who required more than one course of treatment suffered ninety relapses, the majority of which were induced.

Penicillin was prescribed 148 times and fully evaluated in 129 patients. Its cure rate was 41·9 per cent., far below that of the controls. No side-reactions were encountered, but the drug was not prescribed for patients with a history of sensitivity to penicillin.

Streptomycin was prescribed 134 times and fully evaluated 119 times, with a cure ratio of 47·1 per cent., considerably below that of the controls. One patient developed urticaria, chills, fever, and generalized malaise after receiving 1·5 g. of the drug.

Chloramphenicol was prescribed 69 times in the bacterial infections, and evaluated 61 times. It cured 57·4 per cent. of the infections, a rate approximately that of the controls.

It was given 57 times to patients with abacterial infections and evaluated 45 times. By the first course of medication 43 patients were cured, and there was one failure who was given a second course of the drug and cured, so that the cure rate was 100 per cent. Only two out of nine abacterial cases (22·2 per cent.) in the control group were cured spontaneously.

One patient developed an asymptomatic agranulocytosis after 10·5 g. chloramphenicol. His white cell count

dropped from 6,100 to 2,900, but returned to normal in 3 weeks.

Aureomycin cured 79·4 per cent. of 180 patients, this being considerably better than the spontaneous cure rate.

Terramycin cured 70·2 per cent. of 64 patients, this, too, being significantly better than the spontaneous cure rate.

Terramycin and aureomycin produced no untoward side-effects of sufficient severity to cause these drugs to be stopped.

Other Regimes or Factors and Therapeutic Measures.—The sulphonamides and local measures were not evaluated *per se*. Coffee, tea, carbonated beverages, and condiments apparently exercised *no significant influence* on the course of the disease.

Role of Previous Treatment.—Analysis revealed that treatment given before the patient was referred to the 141st General Hospital played an important role in the promptness with which he responded to treatment. The 464 patients treated with antibiotics were divided into six groups :

(1) and (4), the acute and chronic cases admitted without prior treatment ;

(2) and (5), the acute and chronic cases previously treated only for concurrent gonorrhoea ;

(3) and (6), the acute and chronic cases previously treated for non-gonococcal infections.

The acute cases previously treated for non-gonococcal infections had received either short courses of penicillin (300,000 to 1,800,000 units), or penicillin in conjunction with 2 or 3 g. of one of the other antibiotics. In the chronic group, treatment ranged from repeated short courses of assorted antibiotics to antibiotics in conjunction with sounds, prostatic massage, and urethral meatotomy. This group had been previously treated for an average of over 3 months.

Inadequate, empiric, miscellaneous treatment apparently tended to prolong markedly the course of the disease. The variation in relapse rates was equally significant. The relapse rate in the acute, previously untreated group (184 patients, 28 relapses) was only 15·2 per cent., while it was 55·6 per cent. in the acute, previously treated group ; in the chronic, previously untreated group, there were only two relapses in eighty patients (2·5 per cent.), while the chronic, previously treated patients suffered 38 relapses in 98 infections (38·8 per cent.).

A total of 126 relapses were seen, 75 per cent. induced by either liquor or urethral trauma (sounds, cystoscopy). Over half occurred within 2 weeks of completion of treatment, but one did not appear until the middle of the sixth week. Spontaneous relapses developed gradually, and usually consisted of a gross pyuria, some dysuria, and a morning droplet discharge. Induced relapses occurred more abruptly, almost invariably within 24 hrs of the trauma, and were more severe, the discharge often staining the underclothes through the day.

Re-infections.—The reappearance of a profuse and purulent discharge was always viewed with suspicion ; in fact it was considered almost *prima facie* evidence of re-infection, particularly if the patient had already satisfied the criteria for cure. 21 re-infections occurred before the patients had been deemed well, all accompanied by a fresh, concurrent gonorrhoea ; 38 occurred from 1 week to 3 months after a presumptive cure had been achieved. Invariably patients attempted to conceal their derelictions, to persuade the examiner that they were suffering from a relapse. This evasion has given non-gonococcal urethritis the reputation of being more refractory than in fact it is.

DISCUSSION

The clinical picture presented here does not differ substantially from that described by observers since World War II (Harkness, 1950a, b ; Weil and Harris, 1953 ; Willcox, 1949 ; King, 1950 ; Crouch, Reese, and Boudreau, 1953 ; Baier, 1949 ; Abbott, 1950).

Three significant points however must be made :

(1) In approximately three out of five cases the disease will subside spontaneously in 8 weeks ;

(2) The incubation period is virtually identical with that of gonorrhoea (as a corollary, it is highly probable that both diseases are contracted simultaneously, the more virulent gonorrhoea masking the non-gonococcal urethritis) ;

(3) The concurrent gonorrhoea rate in this series was only 17·2 per cent.; Baier (1949) found it to be 46 per cent. in Japan in 1947–48, which can probably be attributed to the later availability of penicillin to Japanese civilians.

The importance of the multi-glass urine test has been emphasized ; and this has been substantiated by others (Harkness, 1950a ; Garvin, 1950 ; Willcox, 1949 ; King, 1950).

Aetiology.—This study sheds little light on the possible cause of the disease in at least one-third of the instances studied here. There can be no question that chloramphenicol attacked a specific entity in the amicrobic infections. Since 62·3 per cent. of 334 " bacterial " infections were cured by one course of therapy, the drug being chosen after *in vitro* sensitivity studies, the probability that a specific agent was attacked must be seriously considered. In only 49·1 per cent. of the controls did the disease subside spontaneously in 4 weeks, a period approximately equivalent to the admini-

stration of one course of medication. On the other hand, 126 other "bacterial" infections did not exhibit this specificity. It should, however, be pointed out that 55 of this group of 126 were individuals who had previously been inadequately treated elsewhere. The possibility, nevertheless, that a third, as yet unidentified, agent was operative in 71 infections and that this agent is not susceptible to the drugs investigated, must be considered.

The source of the infection and the *modus operandi* by which it is disseminated remains unsettled. Herman (1938) suggested the possibility that the disease was auto-infectious, and presented evidence to support this. Although the condom proved to be an effective barrier to gonococcal infections, it offered no impediment to the invasion of agents causing non-gonococcal urethritis. Furthermore, there seems to be no analogous disease in the female. In addition, Helmholz (1950) has demonstrated that the male urethra is the habitat of saprophytes as high as the sixth centimetre segment, enhancing the possibility of auto-infection in some instances.

Specific Therapy.—This study confirmed previous experiences that penicillin (Graham, 1952 ; Babione and Graham, 1952 ; Willcox, 1953) and streptomycin (Willcox, 1953 ; Crouch and others, 1953) are valueless. Reports on both chloramphenicol and aureomycin are contradictory (Willcox, 1953 ; Crouch and others, 1953), but there is considerable agreement on the value of terramycin (Wagner, Morse, and Kuhns, 1953 ; Willcox, 1953 ; Ferguson, Miller, and Herrmann, 1952 ; Willcox and Findlay, 1952 ; Willcox, 1954). Its local use has been recommended by Ferguson and others (1952), but this method of administration has not been studied by others.

Local Treatment.—While local measures were not investigated in this study, collateral evidence has been presented which suggested that these modalities were not merely of little benefit, but probably detrimental. In a like manner, inadequate antibiotic and sulphonamide therapy seemed to prolong the natural course of the disease. Willcox (1954) has presented confirmatory evidence of this last observation.

Recommended Therapy

(1) Terramycin or aureomycin is the recommended antibiotic in a dosage of 250 mg. every 4 hours on a 24-hr basis for 1 week, or a total of 10·5 g.

(2) The progress of the disease should be followed by means of the multi-glass urine test.

(3) The patient should be asymptomatic and free from gross pyuria for a minimum of 2 weeks before inflicting trauma upon the urethra. If there is no relapse following trauma, he is cured.

SUMMARY

(1) Out of a total of 1,943 cases of non-gonococcal urethritis, 588 infections in 529 patients were intensively studied. 440 patients were fully evaluated : in 62 (58·5 per cent.) of 106 controls the disease subsided spontaneously in 8 weeks. 377 out of 378 (99·7 per cent.) were cured by one or more courses of specific antibiotic therapy ; of those so cured 43 were abacterial infections, and 334 bacterial. 97·7 per cent. of the abacterial and 62·3 per cent. of the bacterial infections were cured by one course of medication. The remaining 126 bacterial infections averaged 3·4 courses of medication and required 2 to 7 months to cure.

(2) The probable aetiology of the disease is discussed.

(3) A therapeutic regimen is recommended.

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